



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF

PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

December 19, 2001

MEMORANDUM:

SUBJECT: **Oxyfluorfen.** Response to Comments to the Human Health Risk Assessment.
Reregistration Case No. 2490. Chemical No.111601. DP Barcode D279034.

FROM: Felecia A. Fort, Chemist
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THRU: Whang Phang, Branch Senior Scientist
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TO: Deanna Scher, Chemical Review Manager
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The comments presented below by Dow AgroSciences (DAS) are in response to the Environmental Protection Agency's preliminary Human Health Assessment and Disciplinary Chapters for the Reregistration Eligibility Decision (RED) Document as they pertain to the chemical, oxyfluorfen. The HED Human Health Assessment and the Occupational and Residential Exposure Reregistration Eligibility Decision (RED) documents have been revised to reflect comments and errors noted by the registrant. No changes have been made to the Product and Residue Chemistry Chapter or the Toxicology Chapter. All comments pertaining to drinking water exposures will be addressed by the Environmental Fate and Effects Division (EFED).

General Comments (response prepared by Felecia Fort)

Registrant's Comment: Page 6 Paragraph 1: Delete the word “both” in the sentence beginning “Risk Assessments for aggregate....”

HED Response: The word “both” will be deleted in the revised Human Health Assessment.

Hazard Assessment (response prepared by Kit Farwell)

Registrant Comment Based on the new cancer risk assessment guideline currently used by EPA, oxyfluorfen should not be classified as a Class C animal carcinogen. Furthermore, a NOAEL and safety factor of 100 should be used instead of a Q1*.

HED Response: Although no new studies which might affect the cancer classification for oxyfluorfen have been submitted, HED discussed having a new Cancer Assessment Review Committee (CARC) meeting to see if oxyfluorfen might be re-classified under the new cancer guidelines such that a Q1* would not be needed. The following weight-of-evidence considerations were evaluated.

The tumor response for oxyfluorfen is fairly weak. There are statistically significant increasing trends for increased hepatocellular adenomas, carcinomas, and combined tumors in male mice, only. There is also a statistically significant pairwise comparison for increased combined tumors (adenomas and/or carcinomas) when compared to ethanol-treated controls. Tumor rates for the male mouse combined liver tumors were 2/47, 0/44, 4/44, and 8/52, in the different dose groups.

The mutagenicity studies for oxyfluorfen are essentially negative. However, there are very strong structure-activity relationships. The other diphenyl ether herbicides, all cause liver cancer in mice.

No toxicity or carcinogenicity occurred in the rat combined chronic toxicity/carcinogenicity study at the high dose of 800/1600 ppm. Subchronic rat studies were not supportive of the high dose in the chronic rat study being adequate. A subchronic rat study with the same 71% a.i. technical material used in the chronic rat study found minimal toxicity at 1600 ppm. A subsequent subchronic rat study with the current, 98% a.i. technical material was much less toxic than the older 71% technical material.

The HIARC did not require a new rat combined chronic toxicity/carcinogenicity study because the mouse study was able to determine a Q1* at a lower dose than in the rat study

(and endpoints at lower doses could be selected from chronic dog and mouse studies).

Based primarily upon the very strong structure-activity relationships and the lack of toxicity in the rat study, the Cancer Committee concluded in 1989 that a Q1* was needed based upon the combined tumors in males. The cancer memo said that there was not an increased pairwise comparison when compared to untreated controls. However, after the memo was written, it was determined that the appropriate comparison is to the ethanol-treated controls because ethanol was used in formulating the test diets.

It was concluded that a new CARC meeting is not needed principally because mouse liver tumors occurred with oxyfluorfen, as they do for the other diphenyl ether herbicides and dosing in the rat combined chronic toxicity/carcinogenicity study was inadequate. The negative mutagenicity studies for oxyfluorfen would be supportive of a non-genotoxic mechanism for carcinogenicity if such a mechanism can successfully be demonstrated. Registrants for two diphenyl ether herbicides have conducted or are planning to conduct mechanism studies to demonstrate a mechanism based on peroxisome proliferation. **If the registrant for oxyfluorfen succeeds in demonstrating a non-genotoxic mechanism of carcinogenesis, then a rat combined chronic toxicity/carcinogenicity study at higher doses should be conducted.**

Registrant Comment: The registrant commented that a 28-day inhalation study should not be considered a datagap because it is not required under 40CFR 158.340.

HED Response: The HIARC recommended that a 21-day dermal study in rats and a 28-day inhalation study in rats with 98% a.i. be conducted. The CFR requires a 90-day inhalation study "if use may result in repeated inhalation exposure at a concentration likely to be toxic."

Therefore, a 90-day inhalation study should be required rather than a 28-day inhalation study.

Dietary Exposure (response prepared by Jose Morales)

Registrant Comment: The Agency states that all field trials had non-detectable residues, as did the PDP monitoring data. The Agency therefore should use ½ LOD for all residues after adjustment for percent market share instead of ½ LOQ.

HED Response: HED does not agree that ½ LOD should be used for all residues. HED used ½ LOQ (0.01 ppm) rather ½ LOD (0.003 ppm) for field trial residue values because of the possibility of an occasional residue of oxyfluorfen >0.01 ppm, and the registrant's intention to propose a new single analyte enforcement method (GC/ECD method designated as Method TR-34-95-111) for oxyfluorfen with a quantitation limit of 0.02 ppm.

Occupational and Residential Exposure (response prepared by Timothy Dole)

Response to comments which refer to the Occupational/Residential Exposure(ORE) assessment are addressed in the document "Oxyfluorfen: Response to Phase 1 Occupational/Residential Exposure (ORE) Comments Submitted By Dow Agrosiences on November 1, 2001", Timothy Dole, D279273, 12/4/01).

cc: List B Rereg. File

RDI: WPhang 12/18/2001

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